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Spiro-Pyrrolidine-Catalyzed Asymmetric Conjugate Addition of Hydroxylamine to Enals and 2,4-Dienals

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Abstract: A spiro-pyrrolidine-catalyzed tandem aza-1,4-addition/hemi-acetalization reaction was developed with excellent enantioselectivity (12 examples of $\geq$99% *ee*), and several substrates proceeded with higher *ee* (up to 10% increase) compared with the literature data. Particularly, an interesting and unusual aza-1,6-/oxa-1,4-addition for some substrates was also observed.

Keywords: asymmetric catalysis; aza-1,4-addition; aza-1,6-addition; spiro-pyrrolidines

Asymmetric catalysis, as one of the most useful methods for controlling the enantioselectivity of a chemical transformation, is always an attractive topic in the field of synthetic chemistry. In spite of the achievements in this field, it is also true that there is no catalyst that is universal even for one particular type of reaction. Therefore, developing new catalysts, which can be a beneficial complement for the current catalysts, is always highly desirable. In the case of secondary amine catalysis, pyrrolidine-based catalysts **2** and **3** developed by Jørgensen, Hayashi and MacMillan have shown broad utilities for the asymmetric functionalization of carbonyl compounds *via* the corresponding iminium or enamine activiation mode, which has been recognized as an important part of asymmetric organocatalysis.[1,2] However, it is also hard to see a significant improvement of the stereoselectivities of their analogues by limited changes on the known skeleton.[2c,d,3] Recently, based on our previous research results of the semipinacol rearrangement reaction, spiro-pyrrolidine **1** has been synthesized (Figure 1).[4–6] As such a new type of catalyst possesses two special structural features together, i.e., a chiral pyrrolidine framework and a spiro-skeleton. it is likely that this compound might be used as a complement to current secondary amine organocatalysts through its unique asymmetric induction property, which has been supported by an organocatalytic asymmetric 1,4-conjugate addition.[6] These promising results encouraged us to further explore the catalytic properties of **1**.

A chiral isoxazolidine skeleton, as the key structural moiety, broadly exists in a variety of bioactive molecules (Figure 2).[7] Undoubtedly, the efficient construction of this five-membered ring is certainly a key step for the syntheses of these molecules. Of all the synthetic strategies developed, the organocatalytic asymmetric aza-conjugate addition represents one of the most efficient ways.[8,9] Since the first aminocatalytic intermolecular aza-1,4-addition *via* iminium ion activation was achieved in 2006,[9a] numerous analogous conjugate additions have been developed. In spite of the impressive contributions that have been made in the field of aza-1,4-addition, exploration of more efficient asymmetric catalytic systems to enhance the stereoselectivity is still an important task. Based on our previous research results, it is clear that the secondary amine catalyst **1** showed some special

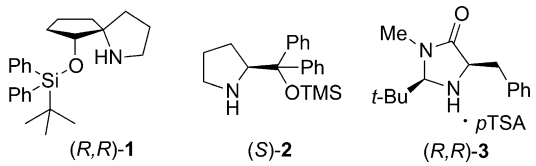


Figure 1. Structure of the spiro-pyrrolidine **1** and other amino catalysts.

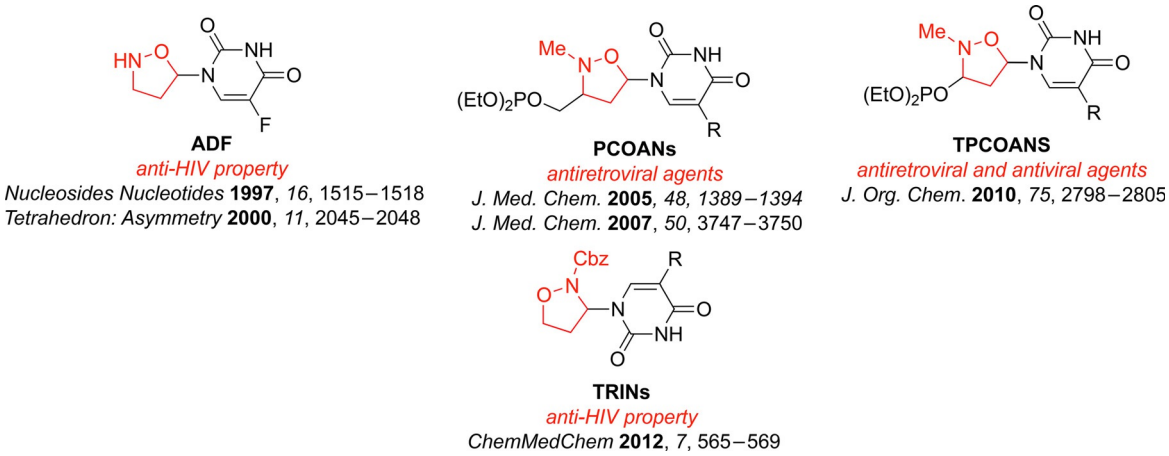
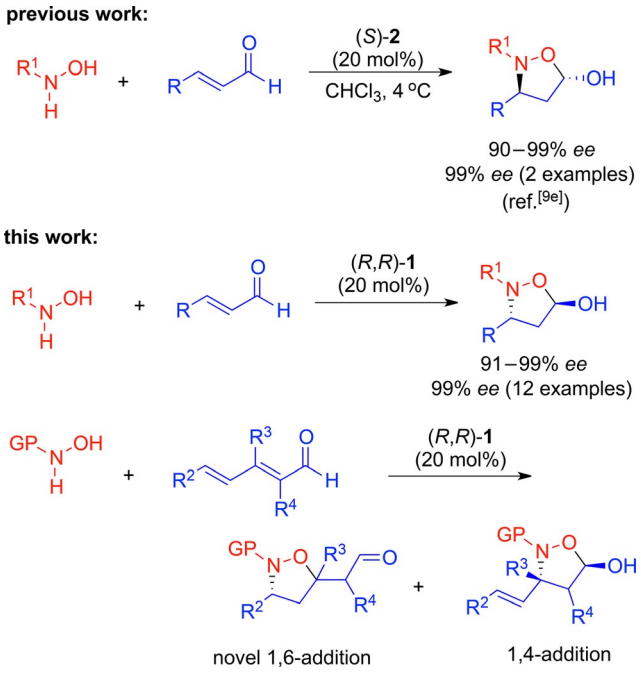


Figure 2. Selected bioactive molecules containing the isoxazolidine skeleton.

stereocontrol properties *via* its unique skeleton,[6] which prompted us to further investigate its efficiency in the asymmetric construction of the isoxazolidine skeleton. In this communication, we report a tandem reaction between *N*-hydroxycarbamates and enals with broad substrate scope and high enantioselectivity (Scheme 1). It is also important to notice that a new tandem reaction consisting of an iminium-type aza-1,6-addition and an oxa-1,4-addition of 2,4-dienals was also developed under the same conditions. To the best of our knowledge, the aminocatalytic asymmetric 1,6-addition to 2,4-dienals remains a challenging task.[10] Further investigations suggested that the regioselectivity depends largely on the substituents at the δ-position of 2,4-dienals.

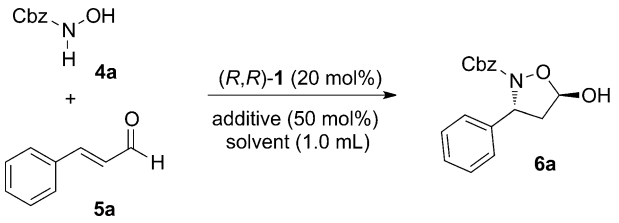


Scheme 1. Strategies for the construction of isoxazolidine skeleton.

Initially, in order to prove the catalytic efficiency of the spiro-pyrrolidine, (*R*,*R*)-**1** was first tested in the asymmetric addition of *N*-Cbz-protected hydroxylamine **4a** to cinnamaldehyde **5a**. Among different solvents investigated, toluene afforded the best result to give the desired product **6a** in 95% yield with 86% *ee* at room temperature (Table 1, entries 1–4). Lowering the reaction temperature to 0 °C could increase the enantioselectivity but led to longer reaction times (Table 1, entry 5). Therefore, an extensive screening of the acid additive was performed to promote the reaction rate, which revealed that benzoic acid was the best choice (Table 1, entry 8) and other substituted benzoic acids had little influence on the *ee* values (Table 1, entries 9–11). The best level of yield (93%) and enantioselectivity (99% *ee*) was achieved when the reaction was conducted at −10 °C with the addition of 50 μL of H_2O, which also acted as a handle for increasing the reaction rate (Table 1, entry 13). In addition, the enantiomer (**6a′**) could be obtained with −99 % *ee* when (*S*,*S*)-**1** was used under the optimized conditions (Table 1, entry 14). When the reaction was performed with a catalyst loading of 10 mol%, product **6a** was obtained with 99% *ee* and 87% yield after 80 h (Table 1, entry 15).

Under the optimized reaction conditions (Table 1, entry 13), the substrate scope of such a reaction was explored for the conjugate addition of *N*-hydroxycarbamates **4** to a variety of β-substituted enals **5** using catalyst (*R*,*R*)-**1**. As listed in Table 2, a variety of β-substituted enals provided the corresponding 5-hydroxyisoxazolidines **6** as a single diastereoisomer with high yields and enantioselectivities. Among the substrates tested, excellent results were achieved for **5** bearing different substitutions at the phenyl group regardless of their electronic properties, giving the adducts **6b–j** with up to 99% *ee* (Table 2, entries 1–8).

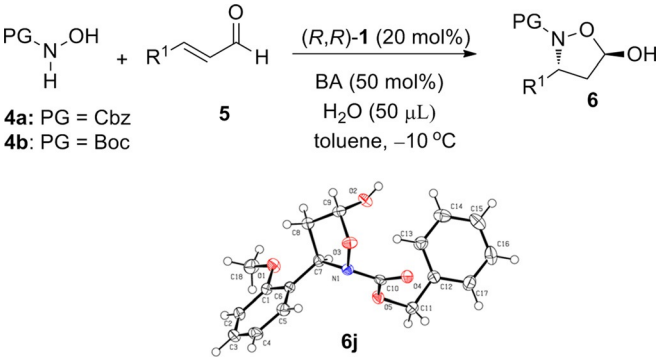
Table 1. Optimization studies for the conjugate addition of **4a** and **5a**.[a]



Entry	Additive	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1[d]	–	25	24	72	85
2[e]	–	25	24	<5	–
3[f]	–	25	24	<5	–
4	–	25	24	95	86
5	–	0	60	93	97
6	PTS	0	48	–	–
7	phenol	0	36	87	95
8	BA	0	18	94	97
9	4-OMeBA	0	18	88	97
10	3-NO_2BA	0	18	82	96
11	2-FBA	0	18	93	97
12	BA	−10	80	87	99
13[g]	BA	−10	48	93	99
14[g,h]	BA	−10	48	90	-99
15[i]	BA	−10	80	88	99

[a] Reactions performed on a 0.125 mmol scale using 1.2 equiv. of **5a**, 20 mol% (*R*,*R*)-**1**, 50 mol% additive in toluene (1.0 mL). BA = benzoic acid.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] In $CHCl_3$ (1.0 mL).
[e] In THF (1.0 mL).
[f] In MeOH (1.0 mL).
[g] H_2O (50 μL) was added.
[h] Catalyst (*S*,*S*)-**1** instead of catalyst (*R*,*R*)-**1**.
[i] 10 mol% (*R*,*R*)-**1** was added

Table 2. Substrate scope of the 1,4-addition reaction.[a]



Entry	4	5 (R^1)	Time [h]	Yield [%][b]	*ee* [%][c]
1	**4b**	Ph	48	95 (**6b**)	>99
2	**4b**	4-ClC_6H_4	48	91 (**6c**)	>99
3	**4b**	4-BrC_6H_4	48	95 (**6d**)	>99
4	**4b**	4-$NO_2C_6H_4$	48	90 (**6e**)	99
5	**4b**	4-$OMeC_6H_4$	60	93 (**6f**)	99
6	**4b**	4-$(NMe_2)C_6H_4$	48	67 (**6g**)	97
7	**4a**	4-ClC_6H_4	48	93 (**6h**)	99
8	**4a**	4-$NO_2C_6H_4$	48	87 (**6i**)	>99
9	**4a**	2-$OMeC_6H_4$	60	88 (**6j**)	>99
10	**4b**	1-naphthyl	48	94 (**6k**)	>99
11	**4a**	2-furyl	60	85 (**6l**)	96
12	**4b**	Bn	48	72 (**6m**)	99
13	**4a**	Me	24	91 (**6n**)	91
14	**4a**	*n*-Pr	36	92 (**6o**)	98
15	**4a**	cyclohexyl	48	82 (**6p**)	99
16	**4a**	CO_2Et	24	91 (**6q**)	96

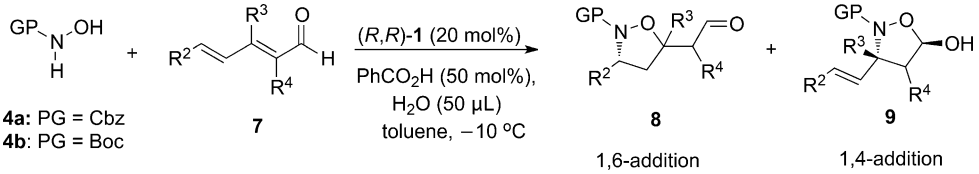
[a] Reactions performed on a 0.125 mmol scale using 1.2 equiv. of **5**, 20 mol% (*R*,*R*)-**1**, 50 mol% benzoic acid, 50 μL H_2O in toluene (1.0 mL) at −10 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.

The enals containing 1-naphthyl as well as 2-furyl groups also performed well to provide **6k** and **6l** with 99% *ee* and 96% *ee*, respectively (Table 2, entries 10 and 11). Additionally, changing the substituent R^1 from an aromatic group to an aliphatic one, benzyl or ethoxycarbonyl, also led to the formation of the desired products **6m–q** with high stereoselectivity (Table 2, entries 12–16). The absolute configuration of **6** was determined by comparison with the literature data and X-ray analysis of racemic **6j** as an example.[9e,11] Remarkably, several reactions of enals, especially 4-chlorocinamaldehyde (Table 2, entry 2), proceeded with the same or higher *ee* (up to 10% increase) with spiro-pyrrolidine **1** compared to the diarylprolinol silyl ether **2** (Table 2, entries 1–4, 14 and 16).[9e]

Encouraged by above results and the remote stereocontrol property of **1**,[6] we then applied catalyst (*R*,*R*)-**1** to the reaction between hydroxylamines and linear 2,4-dienals. To our delight, when 2,4-hexadienal **7a** and *N*-protected hydroxylamine (**4a** and **4b**) were mixed in the presence of catalyst (*R*,*R*)-**1**, a cascade reaction with an aza-1,6-addition as the initial step proceeded smoothly to generate **8a** and **8b**, respectively, with complete regioselectivity (Table 3, entries 1 and 2). In contrast, under the catalysis of chiral pyrrolidine (*R*)-**2**, the reaction of **7a** and **4a** only afforded product **9a**, which involved an aza-1,4-addition as the initial step (Table 3, entry 3). These results indicated the potential catalytic differences between the two types of catalysts, which might bring some complementary effects in their future applications.

As only few methods for organocatalytic enantioselective vinylogous 1,6-additions to linear 2,4-dienals have been developed, and there is no report about the reaction with *N*-protected hydroxylamine, some other δ-substituted 2,4-dienals were subjected to this tandem reaction. With respect to the bulkier δ-ethyl- and δ-*n*-pentyl-substituted 2,4-dienals (**7b** and **7c**), the reaction afforded a mixture of aza-1,6- and aza-1,4-

Table 3. Conjugate addition of 2,4-dienals.[a]



Entry	Substrates	Products	
		1,6-Addition	1,4-Addition
1	**7a**: R^2=Me, R^3=R^4=R^5=H	**8a**: 77% yield,[b] *dr*=2:1,[c] 87/94% *ee*[d]	–
2[g]	**7a**: R^2=Me, R^3=R^4=R^5=H	**8b**: 75% yield, *dr*=2:1,[c] 86/93% *ee*[d]	–
3[h]	**7a**: R^2=Me, R^3=R^4=R^5=H	–	**9a**: 78% yield, *dr*=7:1,[c] 79% *ee*[f]
4	**7b**: R^2=Et, R^3=R^4=R^5=H	**8c**: 50% yield, *dr*=2:1,[c] 87/94% *ee*[d]	**9c**: 26% yield, *dr*>10:1,[e] 91% *ee*[f]
5	**7c**: R^2=*n*-pentyl, R^3=R^4=R^5=H	**8d**: 42% yield, *dr*=2:1,[c] 91/97% *ee*[d]	**9d**: 32% yield, *dr*>10:1,[e] 90% *ee*[f]
6	**7d**: R^2=cyclohexyl, R^3=R^4=R^5=H	–	**9e**: 71% yield, *dr*>20:1,[e] 91% *ee*[f]
7	**7e**: R^2=Ph, R^3=R^4=R^5=H	–	**9f**: 85% yield, *dr*>20:1,[e] 91% *ee*[f]
8	**7f**: R^2=Ph, R^3=Me, R^2=R^4=H	–	–
9	**7g**: R^2=Ph, R^4=Me, R^2=R^3=H	–	–

[a] Reactions performed on a 0.125 mmol scale over 48 h using 1.2 equiv. of **7**, 20 mol% (*R*,*R*)-**1**, 50 mol% benzoic acid, 50 μL H_2O in toluene (1.0 mL) at −10 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by HPLC analysis, details see the Supporting Information.
[e] Determined by ^{1}H NMR analysis.
[f] The *ee* of the major diastereomer of **9** and determined by HPLC analysis.
[g] **4b** instead of **4a**.
[h] Catalyst (*R*)-**2** instead of catalyst (*R*,*R*)-**1**.

addition/cyclization products with low regioselectivity (Table 3, entries 4 and 5). Furthermore, much bulkier δ-cyclohexyl- and δ-phenyl-substituted 2,4-dienals (**7d** and **7e**) gave only aza-1,4-addition/cyclization products (Table 3, entries 6 and 7). As for the formation of products **8** and **9** in different ratios with the use of different substituent R^2, it might be attributed to the subtle variation of the conjugation system of the reaction intermediate. Therefore, the bulkier R^2 was, the higher was the ratio in favor of product **9**. We also tested the reactions of β,δ- and α,δ-disubstituted substrates (**7f** and **7g**),[12] unfortunately, neither aza-1,6-addition nor aza-1,4-addition product was obtained. (Table 3, entries 8 and 9).

In conclusion, spiro-pyrrolidine **1** was found to be a particularly efficient and unique amino catalyst for the tandem aza-1,4-addition/hemi-acetalization reaction between enals and *N*-hydroxycarbamates with excellent enantioselectivities and a broad substrate scope. As a potential complement for current secondary amine catalysts, it could further improve the enantioselectivity of previous excellent results up to 99% *ee*. Also, a new cascade aza-1,6-/oxa-1,4-conjugate addition was observed when these catalytic systems were evolved into some linear 2,4-dienals. Further studies on spiro-pyrrolidine **1** are currently underway.

Experimental Section

Preparation of Isoxazolidines 6

To a solution of catalyst (*R,R*)-**1** (20 mol%, 0.025 mmol), benzoic acid (50 mol%, 0.0625 mmol) and enal **5** (1.2 equiv., 0.15 mmol) in toluene (1.0 mL) at −10 °C were added hydroxycarbamate **4** (1.0 equiv., 0.125 mmol) and H_2O (50 μL). The resulting mixture was stirred for 24–72 h and then the product was purified by flash column chromatography to afford **6**.

Acknowledgements

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